



# Successful treatment with apixaban of sinus venous thrombosis due to pegylated asparaginase in a young adult with T cell acute lymphoblastic leukemia: case report and review of management

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Dear Editor,

A 22-year-old male presented in late 2015 with cough, fatigue, and weight loss. Chest x-ray showed large pericardial effusion, and chest CT confirmed the presence of a large anterior mediastinal mass ( $15.7 \times 19.4 \times 9.7$  cm). Peripheral smear showed numerous blasts, and flow cytometry showed the blasts had a T cell immunophenotype with CD5, CD7, CD3, and TdT positivity. Bone marrow biopsy was consistent with T-lymphoblastic leukemia; microscopic examination of the core biopsy revealed a hypercellular marrow (approximately 90%) with predominantly blasts. Cytogenetic studies were normal. Treatment was initiated per augmented Berlin-Frankfurt-Munster (BFM) pediatric protocol, and he achieved remission after induction with subsequent negative testing for MRD. He received PEG-asparaginase as part of this regimen and after the third dose developed nausea and thumb tingling. His fibrinogen was low at 59 mg/dL (reference range 151–402 mg/dL), and he received one unit of cryoprecipitate. Two weeks later, he woke up with left arm numbness and tingling followed by a 2-min generalized tonic-clonic seizure and left-sided weakness. Brain MRI demonstrated superior sagittal sinus thrombosis with right superior frontal hemorrhagic venous infarct (Fig. 1).

His fibrinogen was low at 77 mg/dL, and he received cryoprecipitate, which was followed by antithrombin (AT) concentrate (AT level 57%, reference range 83–128%) and then heparin infusion. Fibrinogen was checked twice a day with goal of >150 mg/dL. AT was checked every 12 h with a goal of 80%. The heparin infusion was continued for 3 days before transitioning to apixaban (10 mg twice a day to complete a 7-day load, followed by 5 mg bid).

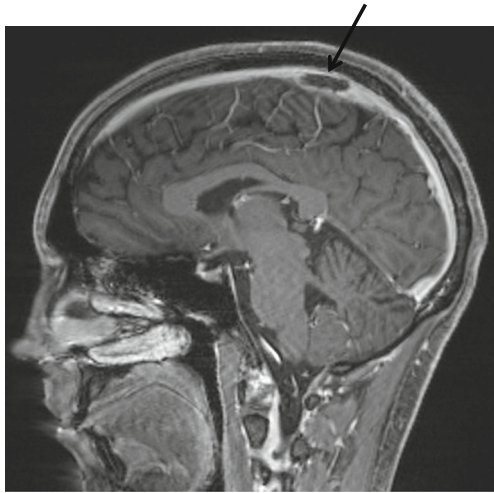
MRI of the brain was repeated 2 months later and showed resolution of the parenchymal edema and the superior sagittal sinus thrombosis. No new dural venous sinus thrombosis was present (Fig. 2). Now, 9 months after his initial presentation, he remains on apixaban without any further neurologic episodes and no major or minor bleeding. He remains in remission and is being treated in maintenance.

The augmented BFM protocol has been utilized in the treatment of children with ALL [1] and has been shown to have efficacy in adults as well [2]. In fact, it has been shown to significantly improve outcomes in young adults such as our patient [3]. Asparaginase is a critical component of the regimen and improves outcomes [4–7]. Asparaginase impairs protein synthesis causing reduced plasma levels of coagulation factors fibrinogen, factor (F) V, FVII, FVIII, FIX, FX, FXI, and  $\alpha_2$ -antiplasmin [8]. This increased bleeding risk is balanced by impairment in the production of anticoagulant proteins antithrombin, protein C, protein S, and plasminogen. Fibrinogen and FVII recovery take place earlier than the recovery of the anticoagulant proteins, and one of the known toxicities of asparaginase is thrombus. The Dana-Farber Cancer Institute [9] found that of 548 patients with ALL treated with some form of asparaginase, and 9% of patients aged 20–30 years developed a venous

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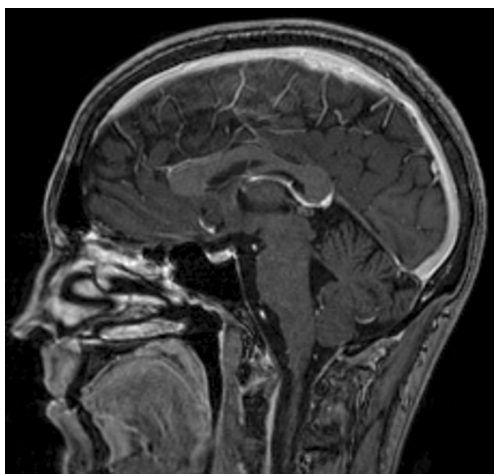
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**Fig. 1** MRI demonstrating superior sagittal sinus thrombosis

thromboembolism (VTE). Two of the 18 adult patients who had VTE had sinus venous thrombosis.

Treatment of asparaginase-related VTE has historically been with heparin or low molecular weight heparin (LMWH). Our patient was treated with a heparin infusion for 3 days, before transitioning to the anti-factor Xa agent apixaban. Long-term recommendations for treatment include LMWH or warfarin. Given the efficacy of apixaban in treating venous thromboses and the low bleeding risk associated with its use when compared to warfarin [10, 11], we opted to treat our patient with apixaban rather than LMWH or warfarin. To our knowledge, this is the first report of the successful treatment with apixaban of a thrombosis associated with PEG-asparaginase administration. Our patient has had an excellent clinical outcome, with resolution of both his neurologic symptoms and venous thrombosis. Further testing of apixaban use in this setting is warranted.



**Fig. 2** MRI after 2 months of treatment with apixaban, showing resolution of superior sagittal sinus thrombosis

**Authors' contributions** L.T. participated in the medical care of the patient, conceived of and designed the report, reviewed the literature, and wrote the manuscript. M.D. provided medical care to the patient and revised the manuscript critically regarding the treatment of ALL. B.G.M. consulted on the medical care of the patient and revised the manuscript critically regarding the management of thrombosis and asparaginase effects. D.O. interpreted the MRIs and selected representative images. All authors read and approved the final manuscript.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Consent** Written informed consent was obtained from the patient for publication of this report.

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#### References

1. Nachman J, Sather HN, Gaynon PS, Lukens JN, Wolff L, Trigg ME (1997) Augmented Berlin-Frankfurt-Munster therapy abrogates the adverse prognostic significance of slow early response to induction chemotherapy for children and adolescents with acute lymphoblastic leukemia and unfavorable presenting features: a report from the children's cancer group. *J Clin Oncol* 15:2222–2230
2. Chang JE, Medlin SC, Kahl BS, Longo WL, Williams EC, Lionberger J, Kim K, Kim J, Esterberg E, Juckett MB (2008) Augmented and standard Berlin-Frankfurt-Munster chemotherapy for treatment of adult acute lymphoblastic leukemia. *Leuk Lymphoma* 49:2298–2307
3. Stock W, Luger SM, Advani AS, Geyer S, Harvey RC, Mullighan CG, Willman CL, Malnassy G, Parker E, Laumann KM, Sanford B, Marcucci G, Paietta EM, Liedtke M, Claxton DF, Foster MC, Appelbaum FR, Erba H, Litzow MR, Tallman MS, Stone RM, Larson RA (2014) Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): early results of U.S. Intergroup Trial C10403. In: Editor (ed) (eds) Book Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia (ALL): Early Results of U.S. Intergroup Trial C10403. Blood, City, pp. 796
4. Dolowy WC, Henson D, Cornet J, Sellin H (1966) Toxic and anti-neoplastic effects of L-asparaginase: study of mice with lymphoma and normal monkeys and report on a child with leukemia. *Cancer* 19:1813–1819
5. Hill JM, Roberts J, Loeb E, Khan A, MacLellan A, Hill RW (1967) L-asparaginase therapy for leukemia and other malignant neoplasms: remission in human leukemia. *JAMA* 202:882–888
6. Sallan SE, Hitchcock-Bryan S, Gelber R, Cassady JR, Frei E 3rd, Nathan DG (1983) Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukemia. *Cancer Res* 43:5601–5607
7. Amylon MD, Shuster J, Pullen J, Berard C, Link MP, Wharam M, Katz J, Yu A, Laver J, Ravindranath Y, Kurtzberg J, Desai S, Camitta

- B, Murphy SB (1999) Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a pediatric oncology group study. *Leukemia* 13:335–342
8. Zakarija A, Kwaan HC (2007) Adverse effects on hemostatic function of drugs used in hematologic malignancies. *Semin Thromb Hemost* 33:355–364
  9. Grace RF, Dahlberg SE, Neuberg D, Sallan SE, Connors JM, Neufeld EJ, Deangelo DJ, Silverman LB (2011) The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols. *Br J Haematol* 152:452–459
  10. Nakamura M, Nishikawa M, Komuro I, Kitajima I, Uetsuka Y, Yamagami T, Minamiguchi H, Yoshimatsu R, Tanabe K, Matsuoka N, Kanmuri K, Ogawa H (2015) Apixaban for the treatment of Japanese subjects with acute venous thromboembolism (AMPLIFY-J study). *Circ J* 79:1230–1236
  11. Goto S, Zhu J, Liu L, Oh BH, Wojdyla DM, Aylward P, Bahit MC, Gersh BJ, Hanna M, Horowitz J, Lopes RD, Wallentin L, Xavier D, Alexander JH (2014) Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: a subanalysis of the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. *Am Heart J* 168:303–309